REMARKS

The present invention relates to the assay of free and complexed troponin isoforms in patient samples. Specifically, the invention describes assay methods and kits that comprise antibodies specific for various cardiac troponin forms. Assays may use an antibody or antibody cocktail that binds to one or more specific troponin form, or that binds all forms. The assay methods and kits of the present invention can be used to diagnose unstable angina and/or myocardial infarction for example.

Claims 85-96, 102-106, and 114-142 are presently pending in the instant application. Applicants have amended claims 87, 88, 90, 93, 96, 105, 116-119, 121-124, 126-129, and 131-133 herein. The amended claims are fully supported by the instant specification, and do not introduce new matter or require a new search. These amended claims are commensurate in scope with the claims as filed, are not amended for purposes of patentability, and are offered solely to assist the Examiner in understanding the claimed invention.

Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer or not yet claimed in one or more applications that may claim priority hereto. Applicants respectfully requests reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non-Art Related Remarks

Personal Interview

The courtesy extended to Applicants' representatives in the personal interview conducted by Examiners Gabel and Le on May 9, 2002 is gratefully acknowledged and appreciated. Applicants provide the following record of the substance of the interview at the Examiners' request.

In the interview, the various rejections under 35 U.S.C. §112, second paragraph were discussed. In addition, the rejections under 35 U.S.C. §§102 and 103, based on Bodor *et al.*, Clinical Chemistry 38: 2203 (1992) were also discussed. The substance of Applicants' comments in regard to these discussions is provided hereinafter. The rejection of the claims under the judicially created doctrine of obviousness-type double patenting, and the requirement for a terminal disclaimer, was also discussed.

35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 85-96, 102-106, and 114-142 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added). *See also*, MPEP § 2173.02 (An examiner "should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness.") (emphasis in original).

"isoform"

The Examiner has indicated that several instances of the term "isoform" should refer to "isoforms." Applicants respectfully disagree that the claims are indefinite in this regard, but submit that the foregoing amendments to the claims render this rejection moot.

"related to"

The Examiner has indicated that several instances of the phrase "related to" are allegedly indefinite, as it is unclear if "related to" refers to "indicative of." As discussed in the personal

interview, the phrase "related to" indicates that the assay signal indicates the presence or amount of the analyte of interest. Applicants respectfully submit that the phrase is not indefinite, and request that the rejection be reconsidered and withdrawn.

"said minimum signal"

The Examiner has indicated that several instances of the phrase "said minimum signal" allegedly lack antecedent support. Applicants respectfully disagree that the claims are indefinite in this regard, but submit that the foregoing amendments to the claims render this rejection moot.

"said antibody..."

The Examiner has indicated that several instances of the phrase "said antibody binding to an equal number of (i) free troponin... which are not said cardiac specific isoform of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoform of troponin; or (iii) a combination of (i) and (ii)" are allegedly indefinite, as the antibody should not bind to these components which are not the target analyte of interest. Applicants respectfully disagree.

As discussed in the personal interview, the claims refer to immunoassays performed with an antibody that specifically binds to one or more target analytes of interest. The skilled artisan will readily acknowledge that such assays often exhibit some background signal, due to residual binding of such antibodies to non-target components of the sample. As a result, the claims to which the Examiner refers are written to describe to the immunoassay as providing a signal from the target analyte(s) that is at least a factor of two larger than the signal provided by a specified set of non-target components.

Because the skilled artisan is reasonably apprised of the scope of the claims with regard to this phrase, Applicants respectfully submit that the phrase is not indefinite, and request that the rejection be reconsidered and withdrawn.

Free cardiac specific troponin I and troponin T

The Examiner has indicated that the phrase "free cardiac specific troponin I and troponin T" is allegedly indefinite, as it is unclear if this intends both free troponin I and free troponin T. Applicants respectfully disagree, but submit that the foregoing amendments to the claims render this rejection moot.

Non-Art Related Remarks

Obviousness-type double patenting

Applicants respectfully submit that the terminal disclaimer, submitted herewith, renders the rejection of claims 85-96, 102-106, and 114-142 as allegedly being unpatentable over claims 1, 3-5, 8, 10-12, and 14-18 of U.S. Patent No. 5,795,725.

35 U.S.C. §§102 and 103

Applicants respectfully traverse the rejection of claims 124-125 and 141 under 35 U.S.C. under 35 U.S.C. 102(b) as being allegedly anticipated by Bodor *et al.*, Clinical Chemistry 38: 2203 (1992). Applicants respectfully disagree that the reference provides each and every element of the claims, as required to establish a *prima facie* case of anticipation.

Applicants also respectfully traverse the rejection of claims 126-128 under 35 U.S.C. 103(a) as allegedly being unpatentable over Bodor *et al.*; and of claims 129-133 and 142 as allegedly being unpatentable over Katus *et al.*, Clinical Chemistry 38: 386 (1992) in view of Bodor *et al.* Applicants respectfully disagree that a *prima facie* case of obviousness has been established.

As discussed by Applicants in the personal interview, the instant claims describe assay methods that use antibodies that specifically bind to free cardiac specific troponin isoforms and that also specifically bind to cardiac specific troponin isoforms in binary and ternary complexes. Applicants respectfully submit that no assays equivalent to those presently claimed, in which

antibody that binds a free cardiac specific troponin isoform, as well as binary and ternary complexes of the isoform, are disclosed in the Bodor *et al.* publication.

Moreover, the skilled artisan would not be motivated to provide such an assay, because, prior to the instant invention, it was not appreciated that such antibodies would be required or advantageous in order to accurately measure cardiac troponin in patient samples. Indeed, prior to the instant application, it was not recognized that failure to consider the complex state of the cardiac-specific troponin isoform could lead to aberrant assay results. Thus, in the absence of the instant specification, no motivation existed for the skilled artisan to modify the Bodor *et al.* publication in order to provide the claimed invention. *See, e.g.*, MPEP § 2143 (The teaching or suggestion to make the claimed combination must be found in the art, and not in the applicant's disclosure); MPEP § 2145(X)(B) (An obvious-to-try situation exists when the prior art gives only general guidance as to the particular form of the claimed invention or how to achieve it).

Similarly, the Examiner cites the Katus *et al.* publication as allegedly disclosing two monoclonal antibodies that bind cardiac specific isoforms of troponin T, contending that "[o]ne of ordinary skill in the art... would have reasonable expectation of success in developing and characterizing monoclonal antibodies that specifically bind free and complexed forms such as those developed and characterized by Bodor." Paper No. 11, pages 6-7. But even if antibodies equivalent to those disclosed in the Bodor *et al.* publication were produced, nothing of record suggests selecting an antibody that binds all forms of a troponin isoform -- including free, binary and ternary complexes of the isoform -- for use in an assay.

In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. §§102 and 103.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address

and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,
FOLEY & LARDNER

Dated: May 17, 2002

By: _____
For Richard J. Warburg,
Michael A. Whittaker
Registration No. 46,230

PO Box 80278
San Diego, CA 92138-0278
Telephone: (858) 847-6721
Facsimile: (858) 792-6773

Appendix A: Marked up amended claims showing changes made. Those claims not amended in the instant response, indicated as "reiterated," are included for the convenience of the Examiner.

85. (Reiterated) An assay for determining the presence or amount of a free and complexed cardiac specific isoform of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds said free cardiac specific isoform of troponin, and which specifically binds said cardiac specific isoform of troponin in a binary complex comprising one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds said cardiac specific isoform of troponin in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin, wherein said signal is at least a factor of two larger than a signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific isoform of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoform of troponin; or (iii) a combination of (i) and (ii), and wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoform of troponin in said sample.

86. (Reiterated) An assay according to claim 85, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

87. (Amended) An assay according to claim 85, wherein said [detectable] signal <u>from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin</u> is at least a factor of five greater than said [minimum] signal <u>resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific isoform of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoform of troponin; or (iii) a combination of (i) and (ii)</u>.

88. (Amended) An assay for determining the presence or amount of [a] free and complexed cardiac specific isoforms of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I and cardiac specific troponin T, and which specifically binds to cardiac specific troponin I and cardiac specific troponin T in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds to cardiac specific troponin I and cardiac specific troponin T in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoforms of troponin, wherein said signal is at least a factor of two larger than a [minimum] signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific isoforms of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoforms of troponin; or (iii) a combination of (i) and (ii), and wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoforms of troponin in said sample.

89. (Reiterated) An assay according to claim 88, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

90. (Amended) An assay according to claim 88, wherein said signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoforms of troponin is at least a factor of five greater than said [minimum] signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific isoforms of troponin; (ii) troponin complexes which do not comprise said cardiac specific isoforms of troponin; or (iii) a combination of (i) and (ii).

91. (Reiterated) An assay for determining the presence or amount of free and complexed cardiac specific troponin I in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I, and which specifically binds to cardiac specific troponin I in a complex comprising at least one other troponin component selected from the group consisting of troponin C and troponin T, and which specifically binds to cardiac specific troponin I in a ternary complex comprising troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin I, wherein said signal is at least a factor of two larger than a signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific troponin I; (ii) troponin complexes which do not comprise said cardiac specific troponin I; or (iii) a combination of (i) and (ii), and wherein said detectable signal is related to the presence or amount of said free and complexed cardiac specific troponin I in said sample.

92. (Reiterated) An assay according to claim 91, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

93. (Amended) An assay according to claim 91, wherein said [detectable] signal <u>from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin I</u> is at least a factor of five greater than said [minimum] signal <u>resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific troponin I; (ii) troponin complexes which do not comprise said cardiac specific troponin I; or (iii) a combination of (i) and (ii)</u>.

94. (Reiterated) An assay for determining the presence or amount of free and complexed cardiac specific troponin T in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin T, and which specifically binds to cardiac specific troponin T in a complex comprising at least one other troponin component selected from the group consisting of troponin C and troponin I, and which specifically binds to cardiac specific troponin T in a ternary complex comprising troponin C and troponin I; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin T, wherein said signal is at least a factor of two larger than a signal resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific troponin T; (ii) troponin complexes which do not comprise said cardiac specific troponin T; or (iii) a combination of (i) and (ii), and wherein said detectable signal is related to the presence or amount of said free and complexed cardiac specific troponin T in said sample.

95. (Reiterated) An assay according to claim 94, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

96. (Amended) An assay according to claim 94, wherein said [detectable] signal <u>from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin T</u> is at least a factor of five greater than said [minimum] signal <u>resulting from said antibody binding to an equal number of (i) free troponin components which are not said cardiac specific troponin T; (ii) troponin complexes which do not comprise said cardiac specific troponin T; or (iii) a combination of (i) and (ii)</u>.

102. (Reiterated) An assay for determining the presence or amount of all free and complexed cardiac specific isoforms of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds all free cardiac specific isoforms of troponin, and which specifically binds all cardiac specific isoforms of troponin in a complex comprising at least one other troponin component selected from the group

consisting of troponin I, troponin C and troponin T, and which specifically binds all cardiac specific isoforms of troponin in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoforms of troponin, wherein said signal is related to the presence or amount of all free and complexed cardiac specific isoforms of troponin in said sample.

103. (Reiterated) An assay according to claim 102, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

104. (Reiterated) An assay according to claim 102, wherein said signal is approximately equal for equal amounts of all cardiac specific isoforms of troponin.

105. (Amended) An assay according to claim 102, wherein said signal is within [a factor of 0.2] 20% for equal amounts of all cardiac specific isoforms of troponin.

106. (Reiterated) An assay according to claim 102, wherein said signal is within a factor of 2 for equal amounts of all cardiac specific isoforms of troponin.

114. (Reiterated) An assay for determining the presence or amount of a free and complexed cardiac specific isoforms of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds said free cardiac specific isoform of troponin, and which specifically binds said cardiac specific isoform of troponin in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds said cardiac specific isoform of troponin in a ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoform of troponin, wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoforms of troponin in said sample.

115. (Reiterated) An assay according to claim 114, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

116. (Amended) An assay according to claim 114, wherein [said] a signal [is approximately equal for equal] detected from said immunoassay for an amount[s] of said free cardiac specific isoform of troponin [and] is approximately equal to a signal detected from said immunoassay for an equal amount of said complexed cardiac specific isoform of troponin.

117. (Amended) An assay according to claim 114, wherein [said] a signal [is within a factor of 0.2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific isoform of troponin [and] is within 20% of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific isoform of troponin.

118. (Amended) An assay according to claim 114, wherein [said detectable] a signal [is within a factor of 2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific isoform of troponin [and] is within a factor of 2 of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific isoform of troponin.

119. (Amended) An assay for determining the presence or amount of [a] free and complexed cardiac specific isoforms of troponin in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I and free cardiac specific troponin T, and which specifically binds to cardiac specific troponin I and cardiac specific troponin T in a complex comprising at least one other troponin component selected from the group consisting of troponin I, troponin C and troponin T, and which specifically binds to cardiac specific troponin I and cardiac specific troponin T in a

ternary complex comprising two other troponin components selected from the group consisting of troponin I, troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific isoforms of troponin, wherein said signal is related to the presence or amount of said free and complexed cardiac specific isoforms of troponin in said sample.

120. (Reiterated) An assay according to claim 119, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

121. (Amended) An assay according to claim 119, wherein [said] a signal [is approximately equal for equal] detected from said immunoassay for an amount[s] of said free cardiac specific isoforms of troponin [and] is approximately equal to a signal detected from said immunoassay for an equal amount of said complexed cardiac specific isoforms of troponin.

122. (Amended) An assay according to claim 119, wherein [said] a signal [is within a factor of 0.2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific isoforms of troponin [and] is within 20% of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific isoforms of troponin.

123. (Amended) An assay according to claim 119, wherein [said] a signal [is within a factor of 2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific isoforms of troponin [and] is within a factor of 2 of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific isoforms of troponin.

124. (Amended) An assay for determining the presence or amount of free and complexed cardiac specific troponin I in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin I, and which specifically binds to cardiac specific troponin I in a complex

comprising at least one other troponin component selected from the group consisting of troponin C and troponin T, and which specifically binds to cardiac specific troponin I in a ternary complex comprising troponin C and troponin T; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin I, wherein said signal is related to the presence or amount of said free and complexed cardiac specific troponin I in said sample.

125. (Reiterated) An assay according to claim 124, wherein said patient sample is selected from the group consisting of a blood sample, a serum sample, and a plasma sample.

126. (Amended) An assay according to claim 124, wherein [said] a signal [is approximately equal for equal] detected from said immunoassay for an amount[s] of said free cardiac specific troponin I [and] is approximately equal to a signal detected from said immunoassay for an equal amount of said complexed cardiac specific troponin I.

127. (Amended) An assay according to claim 124, wherein [said] a signal [is within a factor of 0.2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific troponin I [and] is within 20% of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific troponin I.

128. (Amended) An assay according to claim 124, wherein [said] a signal [is within a factor of 2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific troponin I [and] is within a factor of 2 of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific troponin I.

129. (Amended) An assay for determining the presence or amount of free and complexed cardiac specific troponin T in a patient sample, said assay comprising:

performing an immunoassay with an antibody which specifically binds to free cardiac specific troponin T, and which specifically binds to cardiac specific troponin T in a complex

comprising at least one other troponin component selected from the group consisting of troponin I and troponin C, and which specifically binds to cardiac specific troponin I in a ternary complex comprising troponin I and troponin C; and

detecting a signal from said immunoassay resulting from said antibody binding said free and complexed cardiac specific troponin T, wherein said signal is related to the presence or amount of said free and complexed cardiac specific troponin T ion said sample.

130. (Reiterated) An assay according to claim 129, wherein said patient sample is selected from the group consisting of a blood sample a serum sample, and a plasma sample.

131. (Amended) An assay according to claim 129, wherein [said] a signal [is approximately equal for equal] detected from said immunoassay for an amount[s] of said free cardiac specific troponin T [and] is approximately equal to a signal detected from said immunoassay for an equal amount of said complexed cardiac specific troponin T.

132. (Amended) An assay according to claim 129, wherein [said] a signal [is within a factor of 0.2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific troponin T [and] is within 20% of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific troponin T.

133. (Amended) An assay according to claim 129, wherein [said] a signal [is within a factor of 2 for equal] detected from said immunoassay for an amount[s] of said free cardiac specific troponin T [and] is within a factor of 2 of a signal detected from said immunoassay for an equal amount of said complexed cardiac specific troponin T.

134. (Reiterated) An assay according to claim 85, wherein said antibody is an antibody cocktail.

135. (Reiterated) An assay according to claim 88, wherein said antibody is an antibody cocktail.

136. (Reiterated) An assay according to claim 91, wherein said antibody is an antibody cocktail.

137. (Reiterated) An assay according to claim 94, wherein said antibody is an antibody cocktail.

138. (Reiterated) An assay according to claim 102, wherein said antibody is an antibody cocktail.

139. (Reiterated) An assay according to claim 114, wherein said antibody is an antibody cocktail.

140. (Reiterated) An assay according to claim 119, wherein said antibody is an antibody cocktail.

141. (Reiterated) An assay according to claim 124, wherein said antibody is an antibody cocktail.

142. (Reiterated) An assay according to claim 129, wherein said antibody is an antibody cocktail.